Remarks

Claims 1-18 were pending in the subject application. By this Amendment, claims 1, 3, and 18 have been amended, claims 2 and 14-17 have been cancelled, and new claims 19-25 have been added. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of the applicants' agreement with or acquiescence in the Examiner's position. Accordingly, claims 1, 3, and 18-25 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement (IDS), accompanied by the form PTO/SB/08 and copies of the references listed therein. The applicants respectfully request that the references listed on the form PTO/SB/08 be considered and made of record in the subject application.

As an initial matter, the applicants note that the Information Disclosure Statement (IDS) submitted on March 18, 2005 was not acknowledged in the instant Office Action. The applicants reviewed the status of the subject application on the U.S. Patent Office's Patent Application Information Retrieval (PAIR) system and found that the Patent Office has received the IDS. The applicants respectfully request that the Examiner consider the references listed on the Form PTO/SB/08 and make their consideration of record in the subject application.

By this Amendment, claims 1, 3, and 18 have been amended, and claims 19-25 have been added. Support for the amendments to claim 1 can be found within the specification at page 3, paragraphs [0009] and [0010]; pages 6-7, paragraphs [0030] and [0031]; pages 8-9, paragraphs [0038] and [0039]; page 14, paragraph [0055]; and the claims as originally filed. Claim 2 has been cancelled; therefore, claim 3 has been amended to depend from claim 1, and for clarity. Support for the amendment to claim 18, and support for claim 20, can be found within the specification at page 3, paragraphs [0009] and [0010]; pages 8-9, paragraphs [0038] and [0039]; page 14, paragraph [0055]; and the claims as originally. Support for claim 19 can be found within the specification at

page 4, paragraph [0012]; page 13, paragraph [0053]; page 14, paragraph [0054]; and the claims as originally filed. Support for claim 21 can be found within the specification at pages 3-4, paragraphs [0009] and [0010]; and the claims as originally filed. Support for claim 22 can be found within the specification at page 7, paragraph [0033]. Support for claim 23 can be found within the specification at pages 3-4, paragraph [0010]; page 7, paragraph [0033], and the claims as originally filed. Support for claim 24 can be found within the specification at page 4, paragraph [0012]; pages 8-9, paragraph [0038]; pages 10-11, paragraph [0042]; and page 14, paragraph [0054]. Support for claim 25 can be found within the specification at page 3, paragraph [0009]; page 5, paragraph [0013]; page 13, paragraph [0053]; page 14, paragraph [0055]; and the claims as originally filed.

Claims 1-3 and 18 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description. The applicants traverse and respectfully submit that the subject specification provides a sufficient written description of the claimed invention.

Submitted herewith for the Examiner's consideration are two Declarations under 37 C.F.R. §1.132 by Dr. William G. Kerr, a co-inventor of the subject matter claimed in the subject application. The Declaration dated July 16, 2004 (hereinafter referred to as the Kerr I Declaration), accompanied by Exhibits A-I, and the Declaration dated January 18, 2005 (hereinafter referred to as the Kerr II Declaration), accompanied by Exhibits A-C, were both submitted to the Patent Office in co-pending application serial no. 09/955,174. The Kerr I and Kerr II Declarations include experimental data confirming that interfering RNA may be used to reduce SHIP expression *in vivo*, and only partial reduction of SHIP expression is necessary to result in a physiological change correlating with a therapeutic benefit (in the experiments described in the Kerr I and Kerr II Declarations, the intended therapeutic benefit was rejection of graft rejection).

The subject invention involves reducing SH2-containing inositol-5-phosphatase (SHIP) expression. The mRNA sequences of mouse SHIP-1 and human SHIP-1 have been publicly available since the late 1990s, as evidenced by accession numbers NM_10566 and NM_005541, respectively, from the National Center for Biotechnology Information (NCBI) database. The GenBank sequences show that the mouse and human SHIP sequences were deposited in GenBank by papers published in 1996 and 1997.

Having the structure and sequence of the target gene (SHIP), and the teachings of the specification, the applicants submit that one skilled in the art would readily envision target nucleic acid sequences with the patient's mRNA. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to one skilled in the art to obtain interfering RNA molecules. Therefore, the applicants respectfully submit that the subject specification provides sufficient information regarding the genus of SHIP mRNA and interfering RNA specific thereto. As the Examiner is aware, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known and already available to the public. *In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

RNAi has been demonstrated to facilitate gene silencing in a variety of cell types (primary cells and cell lines) and animal models (see, for example, Tuschl *et al.*, *Mol. Interv.*, 2002, 2(3):158-167, particularly Table 1; Oliveira *et al.*, *Genesis*, 2003, 36(4):203-208; Reich *et al.*, *Molecular Vision*, 2003, May, 9:210-216; Barton *et al.*, *PNAS*, 2002, 99(23):14943-14945; Peng *et al.*, *Cancer Research*, 2002, 62:6400-6404; McManus *et al.*, *J. Immunology*, 2002, 169:5754-5760; Yang *et al.*, 2002, *PNAS*, 99(15):9942-9947; Donze *et al.*, 2002, *Nucleic Acids Research*, 30(10)e46:1-4; and Krichevsky *et al.*, *PNAS*, 2002, 99(18):11926-11929, which are submitted herewith for the Examiner's consideration). Also submitted herewith for the Examiner's consideration are Milhavet *et al.*, *Pharmacol. Rev.*, 2003, Dec., 55(4):629-648), and Kim V.N., *J. Korean Med. Sci.*, 2003, 18:309-318. The Milhavet *et al.*, and Kim publications, along with Agrawal *et al.* (*Microbiol. Mol., Biol. Rev.*, 2003, Dec., 67(4):657-685), which is of record, are review articles citing several earlier papers relating to the design, synthesis, and delivery of interfering RNA molecules. The applicants direct the Examiner's attention to pages 634 to 640 of Milhavet *et al.*, pages 671 to 672 of Agrawal *et al.*, and pages 311 to 314 of Kim. As is made clear from these publications, many laboratories have had significant success in reducing endogenous gene expression in a large variety of cell types,

using various interfering RNA species and delivery methods (see, for example, Table 1 at pages 635-636 of Milhavet *et al.*).

Having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. Due to nucleotide complementarity and the mechanism of RNAi, RNA molecules likely to hybridize with SHIP mRNA and interfere with its expression could then be determined. One of ordinary skill in the art need only be provided with the sequence of the target gene, as opposed to the sequence of any particular interfering RNA. There is no sequence information essential for carrying out the invention that is not provided in the specification or not well known to those skilled in the art. As indicated by Milhavet *et al.*,

> All that is needed to implement siRNA-mediated silencing of expression of a gene of interest is the cDNA sequence of that gene, and commercially available reagents with which to perform the synthesis (Milhavet *et al.* page 637, column 1, lines 2-6).

Not all RNA molecules will inhibit a target gene; however, the availability of target gene sequence information, the capability to synthesize potentially interfering RNA molecules in large quantities, and the availability of criteria for selection of mRNA target sequences increase the likelihood of obtaining gene silencing RNA molecules. As indicated by Kim, "testing 3-4 candidates are usually sufficient to find effective molecules" (page 309, paragraph bridging first and second columns). Thus, while the predictability that any single interfering RNA molecule will be effective is not necessarily high, the probability of identifying an individual functional interfering RNA molecule among candidates is high. Summaries of these criteria for selection of interfering RNA and their mRNA targets are provided in the Agrawal *et al.* (page 671, paragraph bridging the first and second columns) and Milhavet *et al.* (page 637, first column, lines 6-29) publications.

Recognizing that the state of the art has sufficiently developed, the Federal Circuit has held that "the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it ... one of ordinary skill in the art at the time the ... application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious". *In re Wallach*, 71 USPQ2d 1939; 378 F.3d 1330 (CAFC 2004).

The Court also cited the Patent Office's Manual of Patent Examining Procedure (MPEP), which states:

> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. MPEP §2163.II.A.3.a.ii. (8th ed., rev. 2, 2001 and May, 2004).

"Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it." *In re Wallach*, at 1942.

While it is true that sequences and structural formulas provide a convenient method of demonstrating possession of specific molecules, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. For example, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen. Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noelle v. Lederman*, 355 F.3d 1343, 1349; 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and MPEP 2163 IIA3(a). Accordingly, the teaching of the subject specification and knowledge of the sequence and structure of the SHIP gene provides one skilled in the art with sufficient structural and functional correlates to describe the genus of target mRNA and corresponding interfering RNA.

The interfering RNA molecules recited in the claims are not described by function alone. Structural attributes of interfering RNA, including size and content, were known in the art at the time the application was filed. Furthermore, having the nucleotide sequence of the target gene provides

discerning information regarding the sequences (*i.e.*, structural information) of suitable inhibiting interfering RNA molecules, and leads one of ordinary skill in the art to their selection. Accordingly, the teaching of the subject specification, knowledge of the sequence and structure of the SHIP gene, provides sufficient structural and functional correlates to describe the genus of target SHIP sequences and corresponding RNAi molecules.

The written description requirement states that the applicant must describe the invention; it does not state that every invention must be described in the same way. As indicated above, the applicants acknowledge that sequences and structural formulas provide a convenient method of demonstrating possession of many molecules; however, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. Applicants may show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. MPEP§ 2163. In *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 USPQ2d 1609 (Fed Cir. 2002), the Court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed Cir. 2003), the Court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." For example, as indicated above, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). There is no *per se* rule that an actual reduction to practice must occur prior to filing, or that the need to screen for candidate nucleic acid molecules precludes adequate written description of the nucleic acid molecules. Possession may be shown in a variety of ways, including description of an actual reduction to practice, or by showing

that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, *e.g.*, MPEP §2163.02, *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). Compliance with the written description requirement is a fact-based inquiry that will necessarily vary depending on the nature of the invention claimed. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 963; 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

Due to their nature and the state of the art, the interfering RNA molecules recited in the claims are clearly distinguishable from the chemical compounds at issue in *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004), for example, in which the Court affirmed that the description of the cyclooxygenase-2 enzyme (COX-2) and an assay for identifying selective inhibitors of COX-2 did not provide an adequate written description of unknown non-steroidal molecules capable of selectively inhibiting the enzyme. Knowledge of the structure and sequence of the SHIP gene and the state of the art of RNAi provide one skilled in the art with a sufficient structural template and functional correlates to describe the genus of interfering RNA molecules recited in the claims. The subject specification does not require the screening of vast amounts of candidate small molecules *de novo*, based on function alone, with no guidance provided or available as to the molecular structure of a receptor agonist to be identified. The teaching of the subject specification, the knowledge of the sequence and structure of the SHIP gene and protein, and the nature and state of the art of RNAi, together provide sufficient structural and functional correlates to demonstrate possession of the interfering RNA molecules recited in the claims. All functional descriptions of genetic material do not necessarily fail to meet the written description requirement as a matter of law. Rather, the Court has held that the written description requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Enzo Biochem, Inc.* Such is the case here. The written description requirement must be

considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005).

The fundamental concept of the invention is that inhibition of SHIP expression would be of benefit in increasing stem cells, as taught in the subject application. The state of the art was sufficiently developed such that tools and methods for achieving the required inhibition of SHIP expression were appreciated by the inventors, taught in the patent application, and available to those of ordinary skill in the art. Thus, the applicants submit that the patent application contains sufficient disclosure to convey to one of ordinary skill in the art that the applicants had possession of the concept of what is claimed.

The application conveys with reasonable clarity to those skilled in the art that, as of the application's filing date, the applicants were in possession of the genera of interfering RNA molecules used to inhibit SHIP expression, as recited in the claims. Thus, the applicants submit that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicants had possession of the claimed method, which is all that is necessary to satisfy the written description requirement of 35 U.S.C. §112, first paragraph. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 1-3 and 18 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicants respectfully traverse and submit that the claimed invention is fully enabled by the subject specification.

The Office Action indicates that the subject specification does not provide sufficient guidance to teach one skilled in the art to use the interfering RNA molecules targeted to SHIP mRNA *in vivo*, as recited in the claimed methods. To the extent the applicants' remarks set forth above in response to the rejection under 35 U.S.C. §112, first paragraph, for lack of written description, are applicable to the non-enablement rejection, the remarks are incorporated herein by reference. Also submitted herewith for the Examiner's consideration are Gitlin L. and Andino, *J. Virol.*, 2003, 77(13):7159-7165; Coburn G.A. and Cullen, *J. Antimicrobial Chemotherapy*, 2003, 51:753-756; Lieberman J. *et al.*, *Trends Mol. Med.*, 2003, 9(9):397-403; Reich S.J. *et al.*, *Molecular Vision*, 2003, 9:210-216; Scherr M. *et al.*, *Oligonucleotides*, 2003, 13:353-363; and Song E. *et al.*, *Nature Medicine*, 2003, 9(3):347-351, which describe gene silencing using interfering RNA *in vivo*.

As shown by the Milhavet *et al.*, Agrawal *et al.*, Kim, and the other publications submitted herewith, many laboratories have had significant success in reducing endogenous gene expression in a large variety of cell types, using various RNA species and delivery methods (see, for example, Table 1, at pages 635-636 of Milhavet *et al.*). Before and after the subject application was filed, RNAi-mediated gene silencing *in vivo* has been demonstrated in non-human primates (Tolentino M.J. *et al.*, *Retina*, 2004, 24:132-138; Zimmermann T.S., *Nature*, 2006, 441(7089):111-114, which are submitted herewith).

As stated above, having the structure and sequence of the target gene (SHIP), the applicants submit that one skilled in the art could readily obtain target nucleic acid sequences within the patient's mRNA. Furthermore, due to the certainty of the genetic code and complementarity, there is a well known correlation between target nucleic acid sequences within a target gene and nucleic acid sequences that interfere with the expression of the target gene. Hence, having the nucleotide sequence of the target gene provides sufficient information to allow one skilled in the art to obtain candidate interfering RNA molecules without resort to undue experimentation. As shown by the Milhavet *et al.*, Agrawal *et al.*, and Kim publications, having the nucleotide sequence of the target gene provides discerning information regarding the sequences of suitable interfering RNA molecules, and leads one of ordinary skill in the art to their selection. As indicated by Milhavet *et al.*,

> All that is needed to implement siRNA-mediated silencing of expression of a gene of interest is the cDNA sequence of that gene, and commercially available reagents with which to perform the synthesis (Milavet *et al.* page 637, column 1, lines 2-6).

Not all RNA molecules will inhibit a target gene; however, the availability of target gene sequence information, the capability to synthesize potentially interfering RNA molecules in large quantities, and the availability of criteria for selection of mRNA target sequences increase the likelihood of obtaining gene silencing RNA molecules. As indicated by Kim, "testing 3-4 candidates are usually sufficient to find effective molecules" (page 309, paragraph bridging first and second columns). Thus, the probability of identifying effective interfering RNA molecules among candidates is high, and screening for such RNA molecules does not involve undue experimentation.

Furthermore, experimental results demonstrating reduction of SHIP expression by RNAi *in vitro* and *in vivo* using delivery methods taught within the subject specification are described in Exhibits F, G, H, and I, which accompany the Kerr I Declaration. As the Examiner is aware, the determination of enablement must be based on evidence as a whole. As indicated in MPEP § 2164.05, "A declaration or affidavit is, itself, evidence that must be considered" (emphasis in original). MPEP § 2164.05 states:

> To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

Exhibit F shows reduction of SHIP-1 expression in embryonic stem (ES) cells *in vitro* by RNAi. ES cells that express the SHIP-1 gene were transfected with an irrelevant shRNA vector (Lane 3) or with two different shRNA vectors that produced siRNAS specific for SHIP-1 (Lanes 4 and 5). SHIP-1 was detected using an anti-SHIP-1 antibody. As indicated by Dr. Kerr, "Panel A shows significant reduction of SHIP expression in primary ES cells after transfection of SHIP-1-specific shRNA vectors in the absence of selection. It would be expected that these vectors would also interfere with expression of the larger SH2-containing isoforms in differentiated hematopoietic cells." Kerr I Declaration, page 3, section 5.

Exhibit G demonstrates reduction of SHIP-1 expression *in vivo* by RNAi, using techniques taught within the subject specification. Exhibit G shows that induction of SHIP-1 deficiency *in vivo* by RNAi increases the frequency of circulating myeloid cells including cells with a myeloid suppressor cell phenotype. Mice were injected with a SHIP-1 shRNA vector complexed with the cationic lipid 1,2-dioleoyloxy-3-trimethylammonium propane (DOTAP) while two additional mice received an irrelevant shRNA vector specific for the human LRBA gene. The design and sequence of the shRNA vector is shown in Exhibit H.

The mice that received the SHIP-1-specific shRNA vector showed significant suppression of all major SHIP isoforms in the spleen, while β-actin levels were essentially unaltered, as shown in Figure A of Exhibit G. Four different SHIP-1 specific siRNAs were screened for knockdown of SHIP-1 in the RAW264.7 mouse myeloid cell line or ES cells. SiRNAs #1 and #4 were pooled,

complexed with DOTAP and injected intravenously into two separate mice. As with SHIP-1 shRNA-treated mice, there was partial suppression of SHIP-1 expression in peripheral blood mononuclear cells (PBMC) 20 hours after the treatment. Upon examining the impact on the myeloid compartment in PBMC, a significant increase in Mac+Gr1-monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells) was found in the SHIP-1 siRNA treated mice, relative to the GL2 control animals, as shown in Figure B of Exhibit G. The sequences of siRNAs #1-4 and their respective target sites within the open reading frame of mouse SHIP-1 are shown in Exhibit I. As stated by Dr. Kerr, "these findings show that knockdown of SHIP-1 expression *in vivo* by RNAi is a feasible approach that can exert physiological effect even with partial knockdown of SHIP-1 expression." Kerr I Declaration, page 4, section 7.

As explained by Dr. Kerr in the Kerr I Declaration, for the experiment shown in Exhibit G, siRNAs were complexed with DOTAP and injected intravenously into mice. DOTAP is a cationic liposome that has been used for gene delivery to mammalian cells *in vitro* and *in vivo*, as noted above (see, for example, Porteous D.J. *et al.*; Song Y.K. *et al.*).

The applicants respectfully submit that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques which are described in the specification and known to those of ordinary skill in the art, methods for reducing SHIP-1 expression using interfering RNA are fully enabled. At page 5, section 8, of the Kerr I Declaration, Dr. Kerr states:

> Based on the experimental data demonstrating the ability to reduce expression of SHIP-1 *in vivo* in accordance with the teaching of the subject patent application, and the observed effects of SHIP-1 deficiency on NK cell function and GVHD in SHIP-/- transgenic mice (Examples 2-6 of the subject patent application), there is no reason to doubt that reduction of SHIP-1 function by RNA interference or other means of SHIP-1 inhibition will be of therapeutic benefit in suppressing transplant rejection and graft-versus-host disease in mammals, including humans.

Gene silencing using interfering RNA targeting a variety of genes has been demonstrated in animal models of various disease states. An application for patent is not required to show that a claimed method of treatment of a disease condition results in a cure of that disease condition, or even that clinical efficacy is achieved. The Federal Circuit has made it clear that the showing for

therapeutic utility that is sufficient to satisfy the patent laws is not to be confused or equated with the showing required by the Food & Drug Administration for drugs, medical devices, and procedures. *Scott v. Finney*, 32 USPQ2d 1115 (Fed. Cir. 1994) and Manual of Patent Examining Procedure 2164.05. Given the state of the art as demonstrated by the scientific publications submitted herewith, and the information provided in the subject specification and the experimental results obtained therewith, one of ordinary skill in the art can target and reduce expression of SHIP *in vitro* or *in vivo*, without resort to undue experimentation. Thus, the applicants respectfully submit that the subject specification enables the methods as currently claimed.

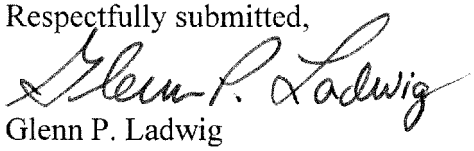
Accordingly, the applicants respectfully submit that, given the teaching of the specification and the state of the art in gene suppression using interfering RNA, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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GPL/mv

Attachments: Petition and Fee for Extension of Time
Supplemental Information Disclosure Statement; form PTO/SB/08; references cited
Copy of Declaration under 37 C.F.R. §1.132 by Dr. William G. Kerr dated July 16, 2004, accompanied by Exhibits A-I
Copy of Declaration under 37 C.F.R. §1.132 by Dr. William G. Kerr dated January 18, 2005, accompanied by Exhibits A-C
Tuschl *et al.*, *Mol. Interv.*, 2002, 2(3):158-167
Oliveira *et al.*, *Genesis*, 2003, 36(4):203-208
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Zimmermann T.S., *Nature*, 2006, 441(7089):111-114